NON-TECHNICAL ABSTRACT

We have demonstrated that the growth of HIV-1 can be blocked by the use of antisense genes. Specifically, we at Enzo designed three antisense genes that interfere with the functioning of two HIV-1 genes essential for virus growth in human cells. In experiments performed outside the body, we tested the effectiveness of these three antisense genes by introducing them into cultured human cells and then exposing these cells to HIV-1. We found that the cells that were producing antisense RNA from these genes were resistant to infection and destruction by HIV-1. This resistance was a stable property of these cells, *i.e.* they were resistant to repeated exposures to HIV-1. The presence of these three genes had no apparent deleterious effect on the cells as indicated by tests that showed the presence of normal levels of cell proteins that characterize these cells as immune cells. When tested separately each of the three antisense genes was effective, but the three together were more effective than any one alone.

In an Enzo-sponsored clinical trial at the Medical School of the University of California at San Francisco our two Principal Investigators Morton J Cowan, M.D. and Marcus Conant, M.D. have put these three genes into blood stem cells. These cells are present in blood, spleen and bone marrow where they serve as a reservoir of progenitor cells that divide and develop into CD4+ cells and other blood cells that are infected by HIV-1. This trial tested whether these altered cells could provide a long-term source for the replenishment of CD4+ and other blood cells. Drs. Cowan and Conant demonstrated that the anti-HIV-1 genes could be successfully put into the stem cells and that the stem cells themselves survived, grew and developed into CD4+ cells for as long as 6 months, the end point of the experiment.

In this present study, Dr. Jeffrey Laurence working with Dr. Michael Schuster of New York Presbyterian Hospital-Cornell Medical Center, New York and Dr. Marcus Conant, of the Medical School of the University of California at San Francisco plan to build upon these results by testing a procedure designed to increase the numbers of cells containing the anti HIV-1 RNA gene. The procedure they plan on testing involves outpatient radiation of the patient subjects coupled with treatment with a course of a medicine that has been.

shown to block the growth of HIV-1. The goal of this study is to produce a continuous and renewable supply of CD4+ cells in large enough numbers to provide a stable immune diversity from only the cohort of cells containing the anti HIV-1 RNA genes.

In the proposed studies hematopoietic stem cells will be collected from the circulating blood of HIV-1-infected individuals. The anti HIV-1 RNA genes will be introduced into each subject's stem cells in the laboratory. At this point the subjects will be irradiated, and the engineered cells will then be introduced back into these individuals. We will study the subjects to determine that this procedure is safe. We will also monitor the cells in each subject's blood for the presence of functioning anti HIV-1 RNA genes for a period of several months. In this way we can determine the stability of the functioning anti HIV-1 genes within the body and the effect of the presence of these genes on the viral load and CD4+ cell count.